ADVERSE EFFECTS OF DRUGS ON EMBRYO AND FETUS

Thesis

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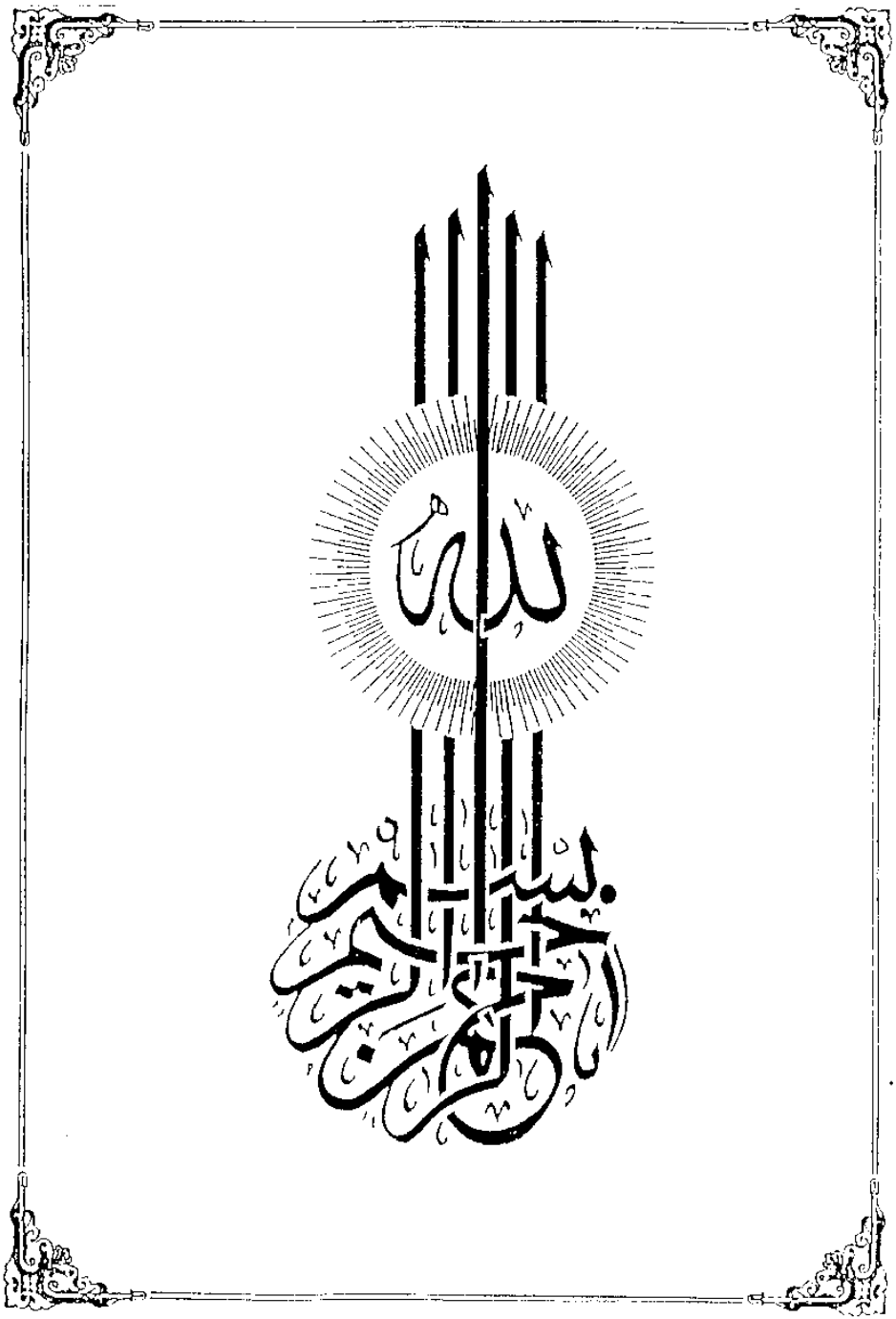

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INTRODUCTION AND AIM OF THE WORK

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In recent years it has become apparent that many drugs given to the mother during pregnancy may have adverse effects on the embryo or foetus, and that the neonate is less able than the adult to metabolize and excrete certain drugs and is thus more susceptible to their undesirable effects (Davies, 1978). This resulted in widespread mistrust among pregnant women of taking any drugs, while physicians have begun to re-examine their prescribing habits, and to realize that the pregnant patient is a very special case in terms of absorption, transport, metabolism and excretion of drugs (Wood and Beeley, 1981).

However, twenty years after the thalidomide disaster teratologists are still not able to provide answers to the questions asked whether a certain drug is safe if taken in early pregnancy or whether another drug which is given to a patient in early pregnancy was responsible for the child's birth defect. This is because animal tests of teratogenicity are simply not accurate predictors of teratogenic effects in man (Hawkins, 1983).

Drugs are not a common cause of congenital abnormality but they are a very important factor (Hawkins, 1983). Other

known teratogens are chemicals, infections, radiation and maternal malnutrition (McNall and Galeener, 1978).

A teratogenic agent produces an alteration in the intrauterine environment so that the developing fetus is either temporarily or permanently injured. If the insult is early and severe, spontaneous abortion occurs. Later in pregnancy, the same insult may cause fetal growth retardation and demise. If the fetus survives the initial insult, it may be so injured or malformed that neonatal death occurs (McNall and Galeener, 1978).

The pregnant woman in the first two weeks after conception frequently is not aware that conception has occured and may interpret the spontaneous abortion as a regular menstrual period. The next six weeks, the stage of embryonic organogenesis, are the most critical. During this time, teratogenic agents are most likely to produce structural or functional abnormalities, because each organ, system or appendage has a critical stage of cellular differentiation during which its development may be deranged (McNall and Galeener, 1978). The period from approximately the eighth week of gestation to term is less critical than the first eight weeks and is thus less vulnerable to the teratogenic effects of various organs (Hawkins, 1983).

Thus, prescribing in pregnancy has become a subject of great importance and the concept of absolute safety of drugs needs to be demolished. Therefore, adherence to the basic rules of prescribing, protect the very great majority of practitioners from either causing harm to a fetus or being accused of doing so. These basic rules are to review all patients with medical disorders before they conceive and encourage them to attend for preconceptional counselling before they become pregnant. The real need for any drug should be questioned and all drug regimens in pregnancy should be reviewed to see how good control can minimise risks. Last but not least is to use agents which have been widely employed in pregnancy for years in preference to new drugs (Hawkins, 1983).

The problem of prescribing drugs in pregnancy has been gravely concerned by the practising obstetrician and physician. Some of the drugs which are frequently used are antiemetics for emesis gravidarum, antihypertensive drugs for preeclampsia, antidiabetic drugs for diabetes etc... .

Thus our aim of work is to throw light on the risk of prescribing any drug during pregnancy and its effect on developing embryo and fetus.

REVIEW OF LITERATURE

DEVELOPMENT OF DIFFERENT SYSTEMS AND ORGANS

The intrauterine period is divided into two periods, the embryonic period and the fetal period. The embryonic period extends from the seventeenth to the fifty sixth day of gestation, during this period organ systems are established and it is during this time that the conceptus is usually most sensitive to teratogenic insult (Kimmel, 1982).

The fetal period extends from the fifty sixth day until birth. This period is characterized by potential viability and legal status may be attained (Rackaway, 1977).

Time of Organogenesis

First week: The fertilized ovum, lying within an envelope called the zona pellucida, undergoes repeated division as it moves along the uterine tube. As it reaches the uterus, it is a hollow ball of cells (blastocyst), which on dissolution of the zona pellucida, attaches to the endometrium and starts implantation (Kimmel, 1981).

Second week: Implantation begins on the sixth or seventh day and is completed by the eleventh day (Rackaway, 1977). During this period, the trophoblast cells comprising the outer shell of the blastocyst, invade the endometrium and gradually facilitate the transfer of substances between mother and embryo (Kimmel, 1981). The trophoblast differentiates into outer syncytio-trophoblast and inner cytotrophoblast. The formation of chorion and chorionic vesicle starts to appear and towards the end of the second week the primary chorionic villi begin to appear (Rackaway, 1977).

Third week: Early in the third week formation of primary chorionic villi is completed and as the week progresses formation of secondary villi occur. At the end of the third week the formation of tertiary or functional chorionic villi is formed. At this week, the bilaminar embryonic disc (of the second week) is changed into the trilaminar disc.

Fourth and Fifth week: This is the critical period of development, where the neural tube is formed and all systems begin to appear, and the cardiovascular system begins to function at this time (Rackaway, 1977).

When the embryonic disc is fully established, it consists of three germ layers known as the ectoderm, the endoderm and the

intraembryonic mesoderm. Ectoderm gives rise to skin, hair, tooth enamel, nails and the nervous system; the endoderm gives rise to the respiratory and alimentary tracts; while the mesoderm gives rise to bones, ligaments, muscles, the cardiovascular system, and most of the urogenital system (Kimmel, 1981).

Development of the central nervous system

The nervous system begins as the neural plate which is formed from the ectoderm of the embryonic disc at about the nineteenth day, this plate will be more differentiated to form a closed tube which will develop to form the brain and the spinal cord.

As the cranial end of the neural tube is closing, three brain vesicles are formed; the prosencephalon, the mesencephalon and the rhobencephalon. The prosencephalon will give rise to the cerebral hemispheres, thalami, posterior lobe of the pituitary gland, pineal body, and optic vesicles. The mesencephalon develops to the brain. The rhombencephalon will divide to give the pons, cerebellum and the medulla oblongata. The rest of the neural tube forms the spinal cord. Meylination starts between the twentieth and twenty fourth weeks of gestation in the cervical portion of the spinal cord. Corticospinal tracts, such as the pyramidal tract

begins to meylinate just before birth, while the human brain is largely meylinated at birth and meylinates slowly until adolescence or later (Barnett, 1969).

Anomalies

1. Anencephaly, which leaves the underlying neural tissue exposed and extroverted. The forebrain and midbrain regions with pituitary and the vault of the skull are most drastically malformed.

2. Spina bifida, which results from failure of a localized fusion of the lips of the neural fold at a certain level in the spinal cord.

3. Absence of, or deficiency within vertebral bodies is very rare to occur.

Development of the eye

Eye formation begins at about the sixth week with the outgrowth from the diencephalon of the optic vesicle which invaginates to form the optic cup. The lens develops from the optic cup. The inner layer of this cup forms the sensory part of the retina while the outer layer forms the pigmented part of the retina. Other components of the eye such as the choroid, cornea, sclera and the extaoccular muscles arise from condensation of the surrounding mesenchyme. The musculature of the iris is said to arise from ectoderm (Beck, Moffat and Lloyd, 1973).

Anomalies

1. Opacity of the lens due to persistence of the hyaloid artery that supplies the lens during intrauterine life.

2. Detachment of the retina if the two embryonic portions of the retina become separated.

3. Congenital glucoma if the canal of Schlemm, which is the venous channel that drains the aqueous humour in the anterior chamber, does not develop.